REMARKS

Claims 1, 3, 4, 7-9, 11, and 47-62 are pending in the subject application, of which claims 47-62 are withdrawn. Applicants have not added, amended, or canceled any claim herein.

Claim Rejections Under 35 U.S.C. § 103(a)—Ho et al. in view of Kent et al.

On page 3 of the Final Office Action, the Examiner rejected claims 1, 3, 4, 7-9, and 11 under 35 U.S.C. § 103(a) as allegedly obvious over PCT International Publication No. WO 01/54701 A1, published August 2, 2001 and naming Ho et al. as "Inventors" ("Ho et al.") in view of PCT International Publication No. WO 00/28003 A1, published May 18, 2000 and naming Kent et al. as "Inventors." The Examiner's purported rationale is set forth on pages 4-5 of the Final Office Action.

Specifically, the Examiner asserted that Ho et al. discloses a method of permitting cessation of antiviral therapy on HIV-infected subjects, without virus rebound or with at least a delayed virus rebound or a decreased post-rebound viral load. The method of Ho et al. allegedly comprises "inducing HIV-specific immune responses by administering an attenuated recombinant poxvirus (e.g., avipox, vaccinia virus, or recombinants thereof) that includes [one] or more nucleic acids encoding one or more HIV-specific immunogens" (citations omitted). However, the Examiner acknowledged that "[a]lthough Ho *et al.* specifically suggests combining an HIV antigen with an immunostimulatory or co-stimulatory molecules such as interleukin 2, which is a cytokine, Ho *et al.* does not disclose co-expressing IFN-γ with an HIV antigen in the poxvirus vector" (citations omitted; underlining added).

Further, the Examiner asserted that "Kent *et al.* discloses an immunogenic construct comprising an avipox virus vector encoding HIV-1 Gag and/or Pol or derivatives thereof and

interferon-gamma (IFN-γ) or a functional derivative thereof that is effective in inducing, enhancing or otherwise stimulating an immune response to HIV Gag and/or Pol" (citations omitted).

The Examiner contends that it would have been obvious to modify the method of Ho et al. so as to replace the poxvirus vector of Ho et al. with the avipox vector of Kent et al., allegedly because one skilled in the art would have been motivated to make such modification to enhance the HIV-specific immune responses by additionally expressing IFN-γ as taught by Kent et al.

In response, Applicants respectfully traverse for at least the reasons set forth below.

The Combined Teachings Are Inadequate

In the first instance, Applicants note that the claimed method is directed to a method A method of reducing or delaying viral rebound during interruption of anti-retroviral drug treatment, wherein the antigen and the IFNγ are expressed in the subject and are effective in maintaining or prolonging a low retroviral load in the subject for a period of time and are effective in reducing or delaying viral rebound during interruption of anti-retroviral drug treatment. The cited references, either taken individually or in combination, simply do not provide adequate teaching for a method that is effective in maintaining or prolonging a low retroviral load in the subject and in reducing or delaying viral rebound during interruption of anti-retroviral drug treatment.

Applicants respectfully disagree with the Examiner's determination that Ho et al. discloses a method of permitting cessation of antiviral therapy on HIV-infected subjects, without virus rebound or with a delayed virus rebound or a decreased post-rebound viral load. As described in Ho et al., when four patients chose to discontinue antiretroviral therapy after

treatment with the protocol summarized above, only two of the four patients exhibited a "delayed rebound" in plasma viremia (page 33, lines 11 to 17).

In this regard, the Examiner's attention is also directed to a report by Markowitz et al. (*Discontinuation of Antiretroviral Therapy Commenced Early during the Course of Human Immunodeficiency Virus Type 1 Infection, with or without Adjunctive Vaccination*, 186 J. INFECT. DIS. 634 (2002), a copy of which was provided in Applicants' Response dated June 8, 2010), which cast doubt on the statistic significance of the observations made by Ho et al. Markowitz et al. discloses that in a experimental trial of the techniques of Ho et al., "[w]hen comparing the characteristics of virus rebound in vaccinated subjects versus subject treated with HAART alone, we could not identify significant differences in the time to virus rebound . . . ." (sentence spanning page 638-39).

Therefore, Applicants respectfully submit that the method of Ho et al. is not effective in permitting cessation of antiviral therapy on HIV-infected subjects, without virus rebound or with a delayed virus rebound or a decreased post-rebound viral load. Thus, the Examiner's reliance on Ho et al. in establishing *prima facie* obviousness is misplaced on this basis alone.

Lack of Motivation To Combine

Applicants also respectfully disagree with the Examiner that those skilled in the art would have been motivated to combine the referenced teachings by modifying the method of Ho et al. to additionally express IFN-γ as taught by Kent in order to enhance the HIV-specific immune response.

In the first instance, while Ho et al. may have proposed to reduce viral rebound by inducing humoral and cell-mediated immunity, the results of Ho et al. are simply inadequate and arguably statistically insignificant for supporting such proposal, as discussed above. Ho et al.

does not comment on why two out of the four patients did not exhibit a "delayed rebound" in plasma viremia, far less offer an explanation of why these patients exhibit a "delayed rebound."

Further, additional failures in attempts to reduce or delay viral rebound by inducing immunity were documented in the art. For example, Rosenwirth (cited in the Office Action dated December 8, 2009) tested the hypothesis that combined drug therapy and therapeutic vaccination would reduce or delay viral rebound after stopping drug therapy in a non-human primate model, and found no evidence of a reduction or delay in viral rebound as a result of therapeutic vaccination (see Figure 1 on page 198 of Rosenwirth). Rosenwirth report that one of two vaccinated Rhesus macaques showed a reduction in viral load after cessation of therapy, while the other macaque exhibited *greater* viral levels after stopping chemotherapy. In addition, one of two control animals receiving PMPA drug therapy alone, also showed rebound followed by a reduction in viral load.

Markowitz et al., *supra*, evidences another attempt, without success, in preventing viral rebound after cessation of retroviral drug therapy by administering ALVACvcp1452 and recombinant gp160 to HIV infected subjects. Despite prolonged drug therapy and apparent suppression of viral replication with or without adjunctive therapeutic vaccination, all subjects experienced virus rebound when treatment was discontinued.

Thus, in light of the lack of a correlation between immunogenicity and viral control during treatment interruption, as reflected by the art, those skilled in the art would not have been motivated to further enhance the immune response against HIV by combining the method of Ho et al. with the teaching of Kent et al., as the Examiner has contended.

Lack of Reasonable Expectation of Success

Even assuming, *arguendo*, that a motivation were found to combine the referenced

teachings, those skilled in the art would still not have had a reasonable expectation of success in arriving at the claimed invention.

In this regard, Applicants note that the experimental protocol of Ho et al. is extremely complex:

i) the virus used is vCP1452, modified to enhance expression of recombinant proteins in mammalian cells (page 28, lines 18-20);
ii) a recombinant gp160 is administered (page 28, lines 22-24); and
iii) the recombinant gp160 is administered in an adjuvant (page 28, 24-26).

Applicants also note the assertion of Ho et al. that "[t]he vaccines being used in this study as well as the adjuvant are novel" (page 28, line 27).

Apart from the questionable statistic significance of the results, as discussed above, the delayed rebound in two of the four patients in Ho et al. were observed after vaccination with *protein* antigens. The Examiner has not established that those skilled in the art would have had a reasonable expectation of success in modifying the method of Ho et al. by administering a nucleic acid vector instead, much less the vector of Kent et al., especially in light of the complexity of the art and the failures by others in the field, as discussed above.

Applicants Have Disclosed Unexpected Results

Applicants note that Ho et al. disclose the "re-induction of HIV-specific *immune responses*" with a purported aim of "achiev[ing] an *immunological control* of persistent infectious virus after discontinuation of antiviral therapy" (page 2, lines 18-21; emphasis added.)

Applicants also note that Kent et al. disclose the following at page 3, lines 15-20 (emphasis added):

> "[A] recombinant viral construct comprising an avipox viral vector or functional derivative thereof which incorporates a first nucleic acid molecule encoding HIV-1 Gag and/or Pol or derivatives thereof and a second nucleic acid

molecule encoding interferon-γ or functional derivative thereof wherein *said recombinant viral construct is effective in inducing, enhancing or otherwise stimulating an immune response to said Gag and/or Pol.*"

In contrast to the combination of Ho et al. and Kent et al., Applicants have disclosed that administration of an avipox vector encoding an HIV antigen and interferon-γ to an HIV-infected subject in the absence of anti-retroviral drug treatment resulted a reduction or delay of viral rebound during interruption of anti-retroviral drug treatment, *in the absence* of a detectable immunological response to HIV (see, for example, the specification of the subject application at page 43, lines 22-25). The Examiner's attention is directed to the results of a clinical trial in humans described in the specification, showing that a pox virus vector encoding *gag* and/or *pol* and interferon-γ achieved a "10 fold reduction in average viral fold" was observed despite of "the lack of any demonstrable immune response in the early part of the trial" (page 43, lines 22-25).

Furthermore, Applicants listed Emery, S., et al., "Randomized, Placebo-Controlled, Phase I/IIa Evaluation of the Safety and Immunogenicity of Fowlpox Virus Expressing HIV gag-pol and Interferon-γ in HIV-1 Infected Subjects," *Hum. Vaccin.* 1(6):232-8 (2005) ("Emery et al.") in a February 12, 2008 Information Disclosure Statement. Applicants respectfully submit that Emery et al. reinforces the disclosure of the subject specification described above. Specifically, Applicants note that in Emery et al., an avipox vector encoding an HIV antigen and interferon-γ administered to an HIV-infected subject in the absence of anti-retroviral drug treatment did not "appear[] to possess detectable T-cell mediated anti-HIV immunogenic properties in HIV infected individuals, as measured by standard T cell assays" (see Abstract).

Therefore, Applicants respectfully submit that they have disclosed, firstly, an avipox vector encoding an HIV antigen and interferon-γ suitable for administration to an HIV-infected subject in the absence of anti-retroviral drug treatment; and, secondly, such administration

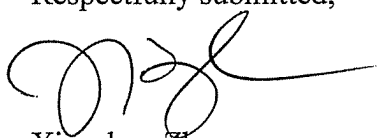
resulted a reduction or delay of viral rebound during interruption of anti-retroviral drug treatment, in the absence of a detectable immunological response to HIV. Applicants respectfully submit that these results were entirely unexpected.

In summary, Applicants respectfully submit that the combination of Ho et al. and Kent et al. does not teach or suggest the subject matter as currently claimed. Therefore, Applicants respectfully submit that claims 1, 3, 4, 7-9, and 11 are not obvious over Ho et al. in view of Kent et al. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

Respectfully submitted,



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